



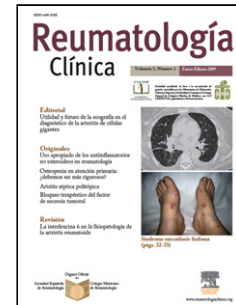
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# Journal Pre-proof

COVID-19 persistente y Encefalomiелitis Miálgica / Síndrome de Fatiga Crónica: similitudes y diferencias

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Long COVID-19 and Myalgic Encephalomyelitis/Chronic Fatigue Syndrome:  
similarities and differences of two peas in a pod

**TITLE PAGE**

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Long COVID-19 and Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: similarities and differences of two peas in a pod

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**SIGNIFICANCE:**

clinical manifestations and pathophysiological features of Long COVID-19 can lead to symptoms commonly presented in patients with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. We present similarities and differences of both entities. Management of both entities may be similar.

Sr. Editor,

Coronavirus disease 2019 (COVID-19) is a highly contagious respiratory disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Prolonged recovery of COVID-19 symptoms, so-called Long COVID-19, has been described even in patients who have mild symptoms and did not required hospitalisation. Various studies showed that at least one out of ten COVID-19 symptomatic patients develop Long COVID-19<sup>1</sup>.

Although there is an absence of a evidence-based clinical practice guidelines neither a clear aetiopatogenesis, a clinical case definition of post-COVID-19 condition was proposed across the International Severe Respiratory and Emerging Infection Consortium (ISARIC) and the World Health Organization (WHO). Long COVID-19 occurs in individuals with a history of probable or confirmed SARS-CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms that last for at least 2 months and cannot be explained by an alternative diagnosis<sup>2</sup>.

Patients may present with a multifaced and marked variability of non-specific symptoms that might be fluctuate or relapse over time. Common symptoms include fatigue, pain, dispnoea, sleep disturbances, physical sequelae, psychological distress, and cognitive impairment but also others which generally have an impact on quality of life. Symptoms may be persist from the initial illness or new onset, following initial recovery from an acute COVID-19 episode<sup>2</sup>. These clinical manifestations can lead to symptoms commonly presented in patients with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS).

ME/CFS is a long-term complicated, heterogeneous, multisystemic and disabling disorder, that was first proposed in 1988 by Holmes et al. to redefine the chronic mononucleosis syndrome as a post-viral fatigue syndrome (PVFS). It is diagnosed according to the 1994 Fukuda criteria, the Canadian consensus document published in 2003 or, more recently, the international consensus criteria of 2011; that offers a review on its physiopathology, symptoms and treatment<sup>3</sup>.

It is characterized by prolonged generalized and abnormal fatigue after exercise and non-remitting significantly with rest, recurrent headache and problems of concentration and memory, which are of recent appearance and that have lasted for at least 6 months. It is

accompanied by such other symptoms as tender lymph nodes, musculoskeletal pain, sleep disruption and psychiatric problems<sup>4</sup>.

Although the cause is unclear, research into the aetiopathogenesis is ongoing. Female sex, type A personality, and family aggregation are established as predisposing factors. Infectious agents (human herpesvirus family), toxicity exposure, and psychological and social experience are associated as precipitating and trigger factors. Other conditions such as advanced age, delay in diagnosis, severe initial involvement, comorbidity, and adaptive disorder are those that maintain the illness once it has become established. Accumulating data indicates a relationship between redox imbalance, mitochondrial dysfunction and oxidative stress pathways in patients with ME/CFS. These abnormalities were also found in patients with Long COVID-19 and suggests that the two disorders may share common pathophysiological features.

However, any potential relationship between ME/CFS and Long COVID-19 is complicated, due to the great heterogeneity of both in its clinical expression and the lack of sensitive screening and standardized instruments to order its different symptoms or agreement regarding the diagnostic criteria. Based on the hypothesis that post-COVID-19 patients can develop a PVFS that is very strikingly similar to ME/CFS, we suggest subgrouping patients with Long COVID-19 into two clinical clustering phenotypes (Table 1).

First cluster, those patients who had mild symptoms and did not require hospitalisation (outpatient care), and develop persistent symptoms after the acute episode, so-called post-COVID-19 fatigue syndrome (PCFS). Many clinical similarities and common pathophysiological features may exist between ME/CFS and PCFS patients (ME/CFS-like).

Second cluster, those patients who required admission to hospital for severe COVID-19 (ICU or non-ICU ward hospitalisation), and develop persistent symptoms after discharge, so-called post-acute COVID-19 syndrome (PACS). Thus, ICU-PACS patients should be differentiated and ICD-10 identified from post-intensive care syndrome (PICS) defining as “new or worsening impairment of cognition, mental Health or physical function after critical illness, persisting beyond the acute care hospitalisation”<sup>5</sup>. Although some differences between ICU-PACS and PICS exist that may likely reflect the variable impact, the symptoms of both entities may be related, *ex aequo*, to immunologic alterations, vasculitis involvement, adverse therapy effects, prolonged immobilisation, and mitochondrial dysfunction.

Taking into account the high grade of evidence of the multidisciplinary treatment programme, composed by the combination of pharmacological treatment based on symptomatology, education, physical exercise and cognitive behavioural therapy, in ME/CFS patients, we believe that the implementation of this follow-up programme might be an effective in Long COVID-19 patients.

In summary, Long COVID-19 should be considered a public Health emergency. Well-conducted studies are needed to identify the real prevalence, phenotypes, risk predictors, future treatments, and the potential differences with ME/CFS and other overlapping pathological entities (PICS).

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Table 1: similarities and differences between Long COVID-19 and ME/CFS

Pathological entities	ME/CFS	Long COVID-19	
		PCFS	PACS
Prevalence	0.5 – 2.5% of general population	10 – 12.2% of COVID-19 patients after acute episode 79% were hospitalized during acute episode (inpatient)	
Gender F/M	4:1	1:1 Male gender is slightly prevalent (56%)	
Age	bimodal incidence 15–20 years 33–45 years	40 – 55 years Mean age 54.4 years	
Aetiology related to infectious agents	HHV (Human Herpesvirus family) SARS-CoV-1 MERS-CoV	SARS-CoV-2	
Patogenesis	Redox imbalance Mitochondrial dysfunction Oxidative stress pathways Abnormal gut microbiota	Direct consequence of viral injury involvement, resulting in ME/CFS-like patogenesis, host cell-mediated immune response mechanism, and neurotropism using a transsynaptic spread mechanism (hypoxic driven neuronal apoptosis)	
	Indirect consequence on mental health due to posttraumatic stress, social isolation, and economic factors, such as loss of employment	Indirect consequence on mental health  PICS-like patogenesis: Adverse therapy effects Prolonged immobilisation Immunologic alterations Vasculitis involvement	
Prolonged symptoms	> 6 months	> 3 months	
Functional Mobility Impairment	+/++	+/++	++/+++
General and constitutional symptoms: fatigue or muscle weakness, joint and muscle pain, flu-like symptoms ...	++	++	++/+++
Pulmonary abnormalities	-/+	-/+	+++
Cardiovascular disorders	-/+	-/+	++/+++
Neurologic symptoms and dysautonomia	+/+++	+/+++	++/+++
Gastrointestinal disorders	++	++	++
Mental Health disorders	++	++	++/+++
Treatment	Follow-up multidisciplinary treatment programme: Pharmacological treatment based on symptomatology Education Physical exercise Cognitive behavioural therapy		



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